Prevalence and risk factors of acquiring *Strongyloides stercoralis* infection among patients attending a tertiary hospital in Thailand

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Objectives: We aimed to determine the prevalence and risk factors for *Strongyloides stercoralis* infection in adult patients attending Siriraj Hospital, a tertiary hospital in Thailand.

Methods: A case–control study was carried out between July 2008 and April 2010. Case and control were identified from 6022 patients for whom results of faecal examination were available. A case was a patient who had *S. stercoralis* larva detected from faecal examination. Control was randomly selected from patients without *S. stercoralis* larvae detected in three consecutive faecal examinations. The proportion of control to case was 2 : 1. Demographic and clinical data for the day of diagnosis and retrospectively up to 15 days preceding the date of faecal examination were reviewed from their medical records.

Results: Overall, 149 (2.47%) patients had *S. stercoralis* larvae positive. There were 105 males (70.5%), with the mean (SD) age of 53.9 (17.2) years. A total of 300 controls were selected. Male gender (odds ratio (OR) = 2.79, 95% confidence interval (CI) 1.78–4.27), human immunodeficiency virus (HIV) infection (OR = 3.23, 95% CI 1.43–7.29), and eosinophilia (OR = 1.81, 95% CI 1.33–2.47) were found to be independent risk factors associated with *S. stercoralis* infection in this setting. Corticosteroid or other immunosuppressive treatment, and other concomitant illnesses were not associated with increased risk of *S. stercoralis* infection.

Conclusion: In this setting, strongyloidiasis was seen more often in male patients with eosinophilia and with HIV infection. Prevention of fatal complication caused by *S. stercoralis* by regular faecal examination, or serology for early detection and treatment of undiagnosed *S. stercoralis* infection, is warranted in these high-risk patients.

Keywords: *Strongyloides*, Risk factors, HIV

Introduction

Strongyloidiasis is a helminth infection caused by *Strongyloides stercoralis*, a nematode endemic in humid, tropical regions including Africa, Southeast Asia, and Latin America.^{1,2} An estimated 30–100 million people are infected by this nematode worldwide.¹ Warm moist temperatures, lower socioeconomic status, and poor sanitation leading to faecal contamination of soil increase risk of strongyloidiasis in the tropics.³ Several risk factors have been associated with *S. stercoralis* infection, including immunosuppressive therapy for rheumatic disease, malignancy, organ transplants, human

immunodeficiency virus (HIV) infection, human T-lymphotropic virus 1 (HTLV-1) infection, diabetes, hypochlorhydria, alcoholism, tuberculosis, malnourishment, chronic obstructive pulmonary disease (COPD), and chronic renal failure.^{4–7}

In individuals at risk, the overwhelming autoinfective cycle can lead to a life-threatening illness due to hyperinfection or disseminated syndrome, with large numbers of larvae affecting the gastrointestinal tract, peritoneum, lungs, and other organs. Sepsis, another complication of severe strongyloidiasis, occurs when enteric bacteria gain access into the extraintestinal sites, either by carriage on the surface of the filariform larvae or by entry through mucosal ulcers induced by the larvae. Mortality of sepsis associated with severe strongyloidiasis could be as high as 12–60%.^{8,9}

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Although there have been many case reports on *S. stercoralis* infection in the literature, few studies have identified the predisposing risk factors for acquiring this infection.^{4,6,7} Given the increasing number of immunocompromised patients worldwide, including Thailand, the objective of this study is to determine the prevalence and risk factors associated with *S. stercoralis* infection in adult patients attending Siriraj Hospital, a tertiary hospital in Thailand.

Material and Methods

Siriraj Hospital is a 2000-bed teaching hospital located in urban Bangkok, central Thailand. This study was part of an open-label, randomized, control trial, conducted between July 2008 and April 2010.¹⁰ The study was approved by the Ethical Committee on Research Involving Human Subjects, Siriraj Hospital, Faculty of Medicine, Mahidol University, Thailand. Written informed consent was obtained from all patients involved in the trial. Results of all stool ova and parasite (O&P) examinations submitted during the clinical trial period were reviewed. We used available routine hospital data, with permission of the hospital's director as part of the clinical trial, to conduct this case-control study.

All stool specimens, submitted for stool O&P examination at this hospital, were fresh specimens. Diagnostic processes included direct examination (wet mount microscopy using saline and D'Antoni's iodine) to identify trophozoite and cyst of protozoan parasites, and when possible at least 2 g of faecal specimen was obtained, and concentration wet mount (using formol-ether concentration technique) to detect eggs and larva of helminths.¹¹ Modified Koga agar culture was performed only in faecal samples obtained from positive patients included in the clinical trial.

The case was a patient who had *S. stercoralis* larvae detected from the faecal examination. During the same period, a control was randomly selected from groups of patients who did not have *S. stercoralis* larvae detected from three consecutive faecal examinations performed within a 30-day period. Exclusion for control was patients with inadequate medical data or no medical record available for reviewing. When a case was identified, random sampling of two controls was done from pools of eligible controls, identified during the same month as the case.

Hospital records were used as data source. They were reviewed for demographic data, signs, and symptoms. Laboratory data were available at the same visit in which stool examination was done (such as complete blood count, blood urea nitrogen, creatinine, total protein, blood sugar, haemoglobin A₁C, CD4 cell count, albumin, and urinalysis). Occupation exposure was classified according to risk of soil and water contact into three groups: (i) high exposure group included

agricultural worker such as rice farmer and gardener, (ii) low exposure group included government officer, housewife, and merchant, and (iii) other occupations were classified as unknown exposure. Other risk factors associated with *S. stercoralis* infection reviewed included HIV infection, corticosteroid use or other immunosuppressive therapy, malignancy, solid-organ or haematological malignancy, organ transplants, diabetes mellitus, COPD, tuberculosis, systemic lupus erythematosus (SLE), nephrotic syndrome (NS), rheumatoid arthritis (RA), and other chronic diseases, such as atherosclerotic heart disease, chronic kidney disease, and hypertension. The presence of concomitant infections, including sepsis, was also recorded in the cases and controls. Alcohol was also not included as a risk factor as history of alcohol intake was not well elucidated in the patient charts. Persistence of diarrhoea for more than 3 weeks period was considered as chronic; otherwise, it was defined acute diarrhoea. After data entry, missing data were checked, and out of range value of any variable was rechecked from hospital data source.

Statistical analysis

The association between various possible risk factors and infection with *S. stercoralis* was calculated as an odds ratio (OR) and 95% confidence interval (CI). Independent risk factors were identified by multiple logistic regression model to adjust for possible risk factors, defined as variables that revealed 95% CI of OR do not include 1 in univariate analysis. All analyses were performed using SPSS programme version 18.0. A *P*-value of less than 0.05 was considered statistically significant.

Results

Overall 9989 stool samples from 6022 patients were tested (8908 faecal samples submitted for first-time evaluation and 1081 faecal samples obtained for follow-up after treatment). Only results of first-time evaluation were included in this analysis. Single faecal sample was obtained from most patients (4094 patients or 68%). Two and three faecal samples were obtained in 970 (16.1%) patients and 958 (15.9%) patients, respectively.

Demographic data, concomitant diseases, and baseline clinical and laboratory investigations of 149 cases and 362 controls are shown in Table 1. Clinical presentations related to strongyloidiasis and laboratory results of the case are shown in Table 2. The most common symptom was diarrhoea; however, more than half of the patients were asymptomatic. All except two patients had an associated medical problem, including concurrent other parasitoses. These patients also had abnormal serum AST and ALT levels, due to their underlying conditions. All cases were treated with either albendazole or ivermectin. Diarrhoea subsided

Table 1 Demographic data and characteristics compared between case and control

Characteristic, n (%)	Case (n = 149)	Control (n = 300)	OR (95% CI)
Male	105 (70.5)	136 (45.3)	2.88 (1.89–4.37)
Median (range) age (years)	51 (22–83)	54 (18–90)	
Age group (years)			
<40	36 (24.2)	73 (24.3)	1
40–64	79 (53)	133 (44.3)	1.18 (0.73–1.9)
≥65	34 (22.8)	94 (31.2)	0.65 (0.38–1.12)
Occupation group			
Low risk	53 (36.9)	145 (48.3)	1
High risk	33 (22.1)	28 (9.3)	3.09 (1.73–5.49)
Unknown	63 (42.3)	127 (42.3)	1.4 (0.92–2.13)
Underlying diseases			
Diabetes mellitus	25 (16.8)	66 (22.0)	0.71 (0.43–1.19)
SLE/NS/RA	23 (14.7)	37 (12.3)	1.30 (0.76–2.27)
Haematologic malignancy	19 (12.8)	61 (20.3)	0.57 (0.33–1.0)
Solid tumour	15 (10.1)	37 (12.3)	0.79 (0.43–1.46)
Glucocorticoid/immunosuppressive treatment	55 (36.9)	117 (32.3)	1.22 (0.83–1.82)
HIV infection	18 (12.1)	10 (3.3)	3.98 (1.79–8.87)
Eosinophilia			
No	83 (55.7)	242 (80.7)	1
>500–1500 (mm ³)	51 (34.2)	33 (11.0)	3.96 (2.48–6.36)
>1500 (mm ³)	15 (10.1)	25 (8.3)	2.02 (1.02–4)

SLE: systemic lupus erythematosus; NS: nephrotic syndrome; RA: rheumatoid arthritis; HIV: human immunodeficiency virus.

after treatment in most patients. Overall, albendazole and ivermectin were well tolerated. The in-hospital mortality was 10%. Causes of death were considered to be related to their underlying disease or its complications (solid tumour, $n = 5$; haematologic malignancy, $n = 3$; diabetes mellitus or systemic lupus erythematosus; or hypertension with complications such as myocardial infarction or sepsis in seven cases). The median duration from admission to death was 2 weeks (range 2–38 weeks).

Among those with available occupational data, cases were more likely to be a farm worker (high-risk population group) but this relationship became insignificant after adjusting with other risk factors. Independent risk factors associated with *S. stercoralis* infection identified by multivariate analysis were male gender (OR 2.79, 95% CI 1.8–4.27), HIV infection (OR 3.23, 95% CI 1.43–7.29), and high eosinophil counts (OR 1.81, 95% CI 1.33–2.47).

Discussion

Strongyloides stercoralis is endemic in many tropical and subtropical areas, and its prevalence varied widely

in Southeast Asia. Previous reports from Thailand showed that prevalence of *S. stercoralis* infection varied widely, ranging between 7.6 and 30.3%.^{12,13} In this tertiary hospital-based setting, the prevalence among adult patients was 2.5%. This positive rate was comparable to the positive rate reported in the literature, using only conventional faecal stool examination.¹ However, this figure is underestimating because this method is not appropriate to diagnose *S. stercoralis* infection.^{1,11} The relatively low prevalence may also be due to different patient population. Siriraj hospital is located in the highly urban Bangkok area where soil-transmitted nematodes are rare. Previous studies were conducted in rural Thailand mainly.¹ Moreover, we did not perform larvae detection by agar plate culture in every patient. This method is more sensitive than conventional stool examination; therefore, false negative is possible in the control group. It is noteworthy that up to one-fourth of our cases were detected only by concentration method. Single stool examination may not be adequate to rule out strongyloidiasis especially in high-risk patients.

In the present study, *S. stercoralis* infection was associated strongly with male gender and HIV infection status. Previous studies from Thailand and India also reported an increased prevalence of strongyloidiasis in males and HIV-infected patients with CD4 count less than 100 mm³.^{7,14} Given the route of transmission, male preponderance could possibly be explained by an increased risk of acquiring infection outdoors.

Both innate and adaptive immune mechanisms are activated in strongyloidiasis. The innate response requires eosinophils to kill *Strongyloides* larvae. Therefore,

Table 2 Symptoms related to *Strongyloides stercoralis* cases ($n = 149$) and baseline laboratory results

Parameters	N (%)
Symptoms	
Diarrhoea	52 (42.6)
Abdominal pain	21 (13.8)
Nausea/vomiting	22 (14.5)
Laboratory test, mean (SD)	
Haematocrit, % (35–45*)	32.6 (7.4)
Eosinophil count, $\times 10^6/L$	8.1 (9.7)
AST, U/L (0–37*)	66.8 (152)
ALT, U/L (0–40*)	42 (44)
Creatinine, mg/dL (0.8–1.2*)	1.3 (1.8)

* Normal laboratory range of Siriraj Hospital.

the finding of significant higher eosinophil count in case than control might be the result of chronic strongyloidiasis rather than risk factor of acquiring this infection.

Diabetes mellitus, use of corticosteroid or other immunosuppressive therapy, solid-organ or haematological malignancy, and other chronic diseases were not associated with increased risk for chronic strongyloidiasis in this study. In addition, we did not find any patient with complicated strongyloidiasis or disseminated infection. Such patients were more likely to have faecal examination and empirical treatment before immunosuppressive therapy; therefore, screening or selection bias of control might be one explanation for these unexpected findings.

Given the low sensitivity of microscopic-based technique for diagnosis of *S. stercoralis* infection, the need for improved diagnostic tests is clear. Several serum antibody detection methods using a variety of antigens have been tested but are still only available in reference laboratories. Sensitivity was reported to be 56–100% depending on antigen used and techniques.¹⁵ The cross-reactivity with other nematode species and difficulty in distinguishing recent from past (and cured) infections remain the major drawbacks of all serologic tests. In countries with a higher prevalence of *S. stercoralis*, serology should be made available and utilized as the better screening tool, particularly in immunocompromised patients or candidates to immunosuppressive treatments. In addition, empirical treatment should be considered in patients at risk of developing *Strongyloides* hyperinfection syndrome or when the prevalence of *S. stercoralis* infection is greater than general population.¹⁶ Current guidelines recommend empirical treatment for strongyloidiasis before haematopoietic stem cell transplantation and solid-organ transplantation for patients with exposure to areas of endemicity, even if results of diagnostic testing are negative.¹⁷

In conclusion, *S. stercoralis* infection was seen more often in males and HIV-infected patients. Prevention of fatal complication caused by *S. stercoralis* by regular faecal examination, for early detection and treatment of chronic strongyloidiasis, is warranted in these high-risk patients.

Disclaimer Statements

Contributors

Funding This study did not receive any funding.

Conflicts of interest There are no conflicts of interest.

Ethics approval The study was approved by the Ethical Committee on Research Involving Human Subjects, Siriraj Hospital, Faculty of Medicine, Mahidol University, Thailand.

Acknowledgements

The work was supported by the grant from Mahidol University, Bangkok, Thailand. The funding agency had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors would like to thank the doctors, nurses, and medical technologists of Department of Medicine, Siriraj Hospital, Faculty of Medicine, Mahidol University for their cooperation and help during the study period.

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